REMARKS

Reconsideration is requested.

The Examiner is requested to confirm that the European Search Report listed on the PTO 1449 Form filed April 16, 2007 and initialed by the Examiner December 28, 2007, has been considered by the Examiner. The list of references cited by the applicant and considered by the examiner indexed in the PTO IFW on January 4, 2008 includes a partial line over the listed reference which may lead to doubt as to whether the listed reference has been considered.

The Examiner is further requested to provide a complete PTO 892 Form, which includes the title of each cited Non-Patent Document.

Specifically, the PTO 892 Form received with the Office Action of January 4, 2008 fails to include the title of each Non-Patent Document.

The Examiner will appreciate that MPEP § 707.05(e) provides as follows:

> 707.05(e) Data Used in Citing References [R-2]
>
> 37 CFR 1.104(d) (see also MPEP § 707.05 and § 901.05(a)) requires the examiner to provide certain data when citing references. The examiner should provide the citations on the "Notice of References Cited" form PTO-892 (copy at MPEP § 707.05). ...
>
> III. < PUBLICATIONS
>
> In citing a publication, sufficient information should be given to determine the identity and facilitate the location of the publication. ...
>
> In citing periodicals, information sufficient to identify the article includes the author(s) and title of the article and the title, volume number issue number, date, and pages of the periodical.

> See http://www.uspto.gov/web/offices/pac/mpep/documents/0700_707_05_e.htm#sect707.05e (August 29, 2007) (Emphasis added.)

The Examiner is requested to provide a new PTO 892 Form which includes the information required by the MPEP, such as is described in the above-quoted passage.

The Examiner is requested to enter a BIB DATASHEET in the PTO IFW which confirms, for example, receipt of the applicants claim for priority benefit as well as the certified copies of the priority documents, as confirmed in the Notice of Acceptance dated February 17, 2008.

Claims 5-10 and 13 are pending.

The objection to claims 5-10 and 13 is obviated by the above amendments. Withdrawal of the objection is requested.

To the extent not obviated by the above amendments, the Section 112, first paragraph "written description", rejection of claims 10 and 13, is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following comments.

Claim 10 has been rejected for failing to satisfy the written description requirement in that the specification allegedly fails to adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising HIF-responsive reporter genes.

The claims refer to a reporter gene including a promoter that comprises a target site recognized by HIF. Support for this recitation can be found, for example, on page 19 of the application. Reporter gene assays are well known in the art and, as such, are

believed to be described in the present specification to the extent that one of ordinary skill in the art will appreciate the applicants were in possession of the claimed invention at the time the application was filed. The application provides exemplification of appropriate systems, including firefly luciferase, secreted alkaline phosphatase and green fluorescent protein, and the Examples illustrate the use of such reporter systems. Further, as discussed on page 41 of the application as filed, constructs comprising a reporter gene and a HIF-recognized promoter are commercially available.

Claim 13 has been rejected for failing to satisfy the written description requirement in that the specification allegedly does not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising conditions required for VDU1 which are capable of stabilizing HIF-α in the absence of a modulator. See page 3 of the Office Action of January 4, 2008.

Claim 13 includes a definition of the test system which is a cell under hypoxic conditions such that the HIF pathway is at a high level of activation whereby VDU1 is capable of stabilizing HIF-α in the absence of a modulator. Support for the recitation may be found, for example, in the first and last paragraphs on page 19 of the application.

The claims are submitted to be supported by an adequate written description and withdrawal of the Section 112, first paragraph, rejection of claims 10 and 13 is requested.

The Section 103 rejection of claims 5-9 over Li (BBRC, Vol. 294, pages 700-709, 2002), Li (JBC, Vol. 277, No. 7, pages 4656-4662, 2002) and Jones (FASEB Journal,

Vol. 16, pages 264-266, 2002), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The present invention is concerned with the provision of a target for *de*ubiquitination by VDU1 and the invention particularly identifies a regulatory pathway present in cells in which HIF-α is stabilized by the action of VDU1. Prior to the present discovery, no target for deubiquitination by VDU1 had been identified and thus no physiological role had been demonstrated.

While the ubiquitination of HIF-α may have been known at the time of filing of the present application (see Maxwell et al., Nature 399:271-275 (1999), Cockman et al., J. Biol. Chem. 275:25733-25741 (2000); Ohh et al., Nat. Cell Biol. 2:423-427 (2000) and Tajinomoto et al., EMBO J 19:4298-4309 (2000) (copies attached)), it was not known at the time of filing of the present application if HIF-α could be *de*ubiquitinated.

The Examiner incorrectly states on page 7 of the Office Action dated January 4, 2008 that "VDU was known in the art to de-ubiquitinate HIF-α, leading to its degradation in the proteosome". The Examiner is requested to specifically indicate where the art of record supports the Examiner's conclusion as none of the art of record teaches that HIF-α could be deubiquitinated by VDU. Furthermore, deubiquitination would *not* lead to the degradation of HIF – rather deubiquitination would stabilize HIF-α and *prevent* its degradation by the proteasome.

Li et al (BBRC) describe a ubiquitin ligase complex comprising VHL, VDU1 and VDU2. However, there is no suggestion of the ubiquitination/deubiquitination of HIF-α. Li furthermore teaches that VDU1 and VDU2 can associate with VHL and that they are

both ubiquitinated for degradation by VHL. However, there is no evidence given as to the natural substrates of VDU1 or VDU2 – all deubiquitination assays were performed using the artificial substrate Ub-GST.

The Examiner particularly cites page 701, page 703, the paragraph bridging pages 705 and 706 and pages 706-708 of Li et al (BBRC). See paragraph spanning pages 5-6 of the Office Action dated January 4, 2008. However, the applicants believe that the cited art fails to teach or suggest the deubiquitination of HIF-α. In fact, on pages 708, Li clearly state that it is not known if either VDU1 or VDU2 can deubiquitinate "downstream targets of pVHL-E3 ligase, such as Hif-1 alpha ..".

As stated by the Examiner, Li et al., (J Biol Chem) teaches that VHL binds to VDU1 and ubiquitinates it for degradation. There is no suggestion that HIF-α is involved in this process and there is no mention of deubiquitination of HIF-α in the cited reference. It is noted that the deubiquitinating activity of VDU1 is demonstrated using an artificial substrate.

Jones et al teach the inability of NSAIDs to increase VHL levels, and therefore decrease HIF-α levels, leading to an inhibition of angiogenesis. There is no teaching or suggestion in the cited reference of deubiquitination reactions.

The Examiner acknowledges that Li (JBC) does not teach the screening of modulators of VDU1 stabilisation of ubiquitination state of HIF-α (see page 6 of the Office Action dated January 4, 2008) and yet believes that it would have allegedly been obvious to have screened for modulators of HIF-α stability (bottom of page 6 of the Office Action). The Examiner is understood to believe that a link between HIF-α

accumulation and deubiquitination was well known in the art – however, none of the cited art supports this conclusion. As discussed above, there was no art before the present application that illustrated the *de*ubiquitination of HIF-α.

While the presence of high levels of HIF-α may have been associated with angiogenesis, this fact alone would not have suggested to the ordinarily skilled person that HIF-α is a target for *de*ubiquitination and would not have motivated the ordinarily skilled person to modulate HIF stability using deubiquitination reactions.

Accordingly, it is submitted that the presently claimed invention would not have been obvious in view of the cited art. Withdrawal of the Section 103 rejection is requested.

The claims are submitted to in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

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